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ORIGINAL INVESTIGATION

Examination of the effect of acute levodopa administration on the loudness dependence of auditory evoked potentials (LDAEP) in humans

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Abstract
Rationale The loudness dependence of the auditory evoked potential (LDAEP) is considered a noninvasive in vivo marker of central serotonergic functioning in humans. Nevertheless, results of genetic association studies point towards a modulation of this biomarker by dopaminergic neurotransmission.
Objective We examined the effect of dopaminergic modulation on the LDAEP using L-3,4-dihydroxyphenylalanine (levodopa)/benserazide (Madopar®) as a challenge agent in healthy volunteers.
Methods A double-blind placebo-controlled challenge design was chosen. Forty-two healthy participants (21 females and 21 males) underwent two LDAEP measurements, following a baseline LDAEP measurement either placebo or levodopa (levodopa 200 mg/benserazide 50 mg) were given orally. Changes in the amplitude and dipole source activity of the N1/P2 intensities (60, 70, 80, 90, and 100 dB) were analyzed.
Results The participants of neither the levodopa nor the placebo group showed any significant LDAEP alterations compared to the baseline measurement. The test–retest reliability (Cronbachs Alpha) between baseline and intervention was 0.966 in the verum group and 0.759 in the placebo group, respectively.
Conclusions The administration of levodopa showed no effect on the LDAEP. These findings are in line with other trials using dopamine receptor agonists.

Keywords Dopamine · Loudness dependence auditory evoked potentials (LDAEP) · Levodopa · Primary auditory cortex · Serotonin

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Introduction

Reliable methods for the in vivo assessment of the central serotonergic system would be of great interest for the understanding of neuropsychiatric disorders and for monitoring the therapeutic efficacy of pharmacological treatments (Hegerl and Juckel 2000). Parameters regarding peripheral serotonin (5-HT) metabolism such as the concentration of 5-hydroxyindolacid in cerebrospinal fluid or the 5-HT transporter (SERT) availability in thrombocytes do not properly reflect central 5-HT functioning. They merely state inconsistent snapshots. In contrast to this, the loudness dependence of auditory evoked potentials (LDAEP) has been reported to be a measure of central 5-HT activity in humans (Hegerl et al. 2001; Hegerl and Juckel 1993, 1994;

Juckel et al. 1997; Kawohl et al. 2008b; O'Neill et al. 2008a). A pronounced LDAEP supposedly reflects a low central 5-HT neurotransmission and vice versa.

Nevertheless, the issue of specificity of the LDAEP for the 5-HT system has been the topic of debate. Several findings cast some doubt over its sensitivity to changes in 5-HT functioning alone (Juckel et al. 2008b, 1997; O'Neill et al. 2006; Pogarell et al. 2004; Uhl et al. 2006). An association between 5-HT (SERT) and dopamine (DAT) transporter availability and the interindividual LDAEP has been found in a [123I]beta-CIT single-photon emission computed tomography (SPECT) study (Pogarell et al. 2004). High availability of the transporter enzymes, indirectly suggesting reduced 5-HT and dopamine in the synaptic cleft, was correlated with an increased LDAEP in patients with obsessive–compulsive disorder. Dopaminergic influence onto the LDAEP was stated. Lee at al. (Lee et al. 2010) found the LDAEP to be positively associated with DAT in a trial with 49 healthy volunteers using SPECT to approximate the availability of dopamine transporters and serotonin transporters. After adjusting for age and gender, the LDAEP was negatively associated with SERT. Further evidence for the possible involvement of dopamine in the genesis of LDAEP was stated.

A recent genetic association study has revealed an association between single nucleotide polymorphisms (SNPs) in the gene coding for the dopamine degrading enzyme catechol-O-methyltransferase (COMT) and the LDAEP (Juckel et al. 2008b). COMT is involved in the inactivation of synaptic dopamine (Axelrod and Tomchick 1958). Functional SNPs in the *COMT* gene result in attenuated dopamine catabolism, and several findings point to a modification of the risk for psychotic disorders by these genetic variants (Funke et al. 2005; Meyer-Lindenberg and Weinberger 2006; Nicodemus et al. 2007). Another genetic association study revealed an association between the functional SNPs in genes coding for nitric oxide synthase (NOS): single nucleotide polymorphisms in both *NOS1*- (G-84A_exon 1c promoter polymorphism) and *NOS3* gene (Glu298Asp) are associated with a lower LDAEP. NOS is an enzyme catalyzing the production of nitric oxyde (NO) from L-arginine. NO is a gaseous molecule with neurotransmitter properties that also interacts with dopaminergic transmission (Kawohl et al. 2008a).

The aforementioned studies point to a dopaminergic influence on the LDAEP. However, O'Neill et al. (O'Neill et al. 2006) could not find a significant effect on the LDAEP after dopaminergic stimulation of the $D_1/D_2/D_3$ receptors with pergolide and D_2/D_3 receptors with bromocriptine. In another trial of the same study group, selective serotonin and dopamine depletion with greater than 80% plasma precursor depletion had no effect on the LDAEP (O'Neill et al. 2008b).

Despite of O'Neill et al.'s findings we developed a dopaminergic challenge with a naturalistic agent. Synthetic dopamine receptor agonists, as used in the aforementioned studies, exhibit different receptor affinities compared to dopamine. In contrast, we decided to use the prodrug levodopa due to its more naturalistic action via synaptic dopamine; levodopa is the precursor of dopamine. It is decarboxylized to dopamine, which cannot pass the blood–brain barrier. Compared to synthetic agonists, levodopa bares a decisive advantage in inducing dopaminergic stimulation; after decarboxylation, levodopa acts as a transmitter itself, thus modulating the dopaminergic effect in the most naturalistic manner. In contrast to a synthetic agonist, such as, bromocriptine, specific receptor affinities do not have to be taken into account. Several trials have shown an increase of synaptic dopamine level due to oral intake of levodopa and benserazide (de la Fuente-Fernandez et al. 2004; Floel et al. 2005; Khor and Hsu 2007; Kumakura et al. 2004). In addition, we wanted to compute the EEG data with the dipole source model to differentiate between the primary and secondary auditory area. The primary auditory area is considered to be the generator of the LDAEP signal (Hegerl and Juckel 1993, 1994; Hegerl 1994; Hegerl et al. 1994). Hence, the aim of this study was to investigate the influence of acute dopaminergic stimulation on the LDAEP in healthy individuals with a challenge agent not used so far. We hypothesized that the acute synaptic dopamine excess caused by levodopa intake leads to an intraindividual decrease of the LDAEP.

Methods

Participants

Healthy volunteers were selected among the staff and with the help of the volunteer server of the Psychological Institute of the University of Zürich. Normal hearing was tested clinically.

The 42 healthy participants had not been treated for any psychiatric disease in their lifetime and had no first-degree relatives with psychiatric disorders. All participants were drug free (except oral contraceptives) and were asked to abstain from alcohol the day prior to the session. Caffeine and nicotine intake were permitted to avoid withdrawal symptoms. Four female and six male participants were cigarette smokers. The volunteers were examined for existing contraindications against the intake of levodopa 200 mg/benserazide 50 mg and domperidone 20 mg by standard blood tests and electrocardiography. Psychiatric and somatic illnesses were excluded by psychiatric and physical examination by a physician trained in somatic and psychiatric

medicine. A pregnancy test was carried out in female volunteers before participating in the trial.

Forty-two healthy subjects (21 females, 21 males; mean age placebo group, 34 years; mean age verum group, 33 years; SD 9.9; 7.8 respectively) attended in this trial.

Ethical issues

The study was carried out in compliance with the Declaration of Helsinki and was approved by the ethics committee of the Canton of Zurich including the specialized sub-commission for neuroscience. All subjects gave written informed consent and were paid customary expenses.

Study design and procedure

The study used a randomized double-blind placebo-controlled challenge design. Each subject underwent LDAEP measurement under two different conditions: (1) baseline and (2) placebo or levodopa/ benserazide. The levodopa/benserazide dosages were selected according to the literature. Significant behavioral drug effects occur under 200 mg levodopa and 50 mg benserazide (Black and Mink 2000; Floel et al. 2005; Micallef-Roll et al. 2001). After 8 h of fasting (Black and Mink 2000) in order to exclude proteinous inhibition of the enteral levodopa absorption, the participants arrived on the testing days at 8 o'clock in the morning and ate a low protein breakfast (bread with butter and jam, orange juice). In order to reduce the likelihood of any nausea following levodopa/benserazide intake, domperidone 20 mg was given orally (O'Neill et al. 2006). Domperidone does not cross the blood/brain barrier and acts as a peripheral dopamine antagonist (O'Neill et al. 2006). Afterwards, a baseline LDAEP-recording was performed. After this recording, levodopa/ benserazide in a dosage of 200 mg/50 mg or placebo were applied orally. Both levodopa and placebo were given in cachets that were not distinguishable, neither by the staff nor the participants. The cachets had been labeled, listed, and stored by a person independent to the trial staff. The number of the cachet given to the volunteer was listed. At the estimated t_{max} of levodopa (Floel et al. 2005) of 60 min after oral intake the second measurement was conducted. Blood pressure and pulse were measured before the intake of the agent and after the last LDAEP recording. The participants were given two further dosages of domperidone 10 mg for intake, if required, at noon and in the evening to prevent nausea after the trial.

Data acquisition

Participants were seated upright in a comfortable chair with their eyes open. They were instructed to relax throughout the recording and to avoid facial muscle movement. Paying attention to the auditory stimuli has been shown to modulate the intensity of evoked potentials in humans (Baribeau and Laurent 1987). In order to distract the participants, a silent movie was shown during the presentation of the auditory stimuli.

Electrophysiological measurements

EEG data were recorded using a BrainAmp amplifier and the Brain Vision Recorder software (Brain Products GmbH, Munich, Germany). Electrodes were applied to the scalp using a carefully positioned nylon cap (BrainCap 32 standard with 32 channels (Easycap, Herrsching-Breitbrunn, Germany)) in accordance with the International 10/20 System. Scalp electrode impedances were kept below 10 kΩ. The evoked responses were recorded with 32 electrodes referenced to Cz (32 channels). Sinus tones (1,000 Hz, 40-ms duration with 10-ms rise and fall time, ISI randomized between 1,800 and 2,400 ms) of 5 intensities (60, 70, 80, 90, 100 dB sound pressure level, generated by a PC-stimulator that was calibrated in the Department of clinical audiology of the University of Zürich) were presented binaurally via headphones in a pseudo-randomized order using Presentation software (Neurobehavioral Systems, Inc., San Pablo, CA). Data were collected with a sampling rate of 1,000 Hz and a band pass filter of 0.5–80 Hz.

Event related potential processing

Periods of 100 ms pre stimulus and 300 ms post stimulus time were evaluated for each of the five intensities with a total of 350 sweeps. Before averaging, the first responses of each of the five intensities were excluded in order to reduce short-term habituation effects. For artifact suppression, all trials were automatically excluded from averaging when the voltage exceeded ±50 μV in any one of the 32 channels at any point during the averaging period. For each participant, the remaining sweeps were averaged separately for the five intensity levels.

Dipole source analysis

A dipole source analysis (DSA) was computed with the data of the resulting auditory evoked potentials N1 and P2 using the analysis and visualization software BESA® (version 5.1.8, MEGIS, Gräfelfing, Germany). DSA provides a high spatio-temporal accuracy (Kawohl et al. 2007; Waberski et al. 2003). A grand average over all subjects was calculated. On the basis of this grand average a dipole model was computed for the 60 and 70 dB intensities with two regional sources (one for each hemisphere) (Fig. 1).

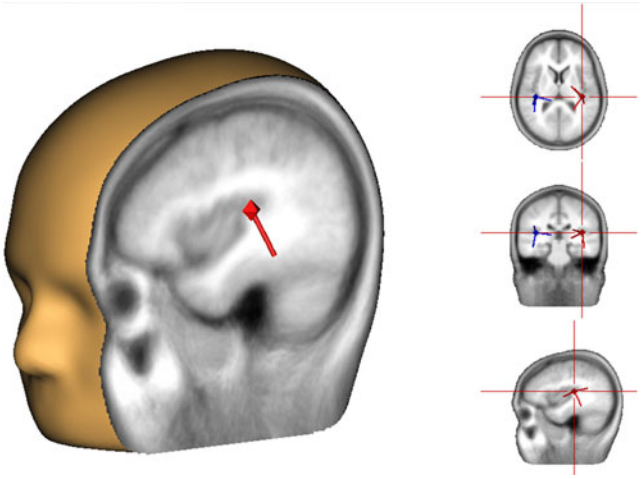

Fig. 1 Symmetrical dipole sources of auditory evoked potentials following stimulation with 70 dB localized in Brodmann area 41 (primary auditory cortex, Talairach coordinates −38, −25, 11 and 38, −25, 11)

Another dipole model was computed for the 80, 90 and 100 dB intensities and a third regional source was added in the frontal region. A total of six equivalent dipoles for each evoked potential was computed. The tangential dipoles 1 and 3 represented the generators of the evoked potentials localizing in the primary auditory cortex. Dipoles 2 and 4 represent the generators in the secondary auditory cortex. The source waveforms of dipole 1 and 3 were used to compute the loudness dependence. The methods have been published in detail (Hegerl and Juckel 1993; Hegerl 1994; Hegerl et al. 1994; Hegerl and Juckel 1994). Additionally, N1 and P2 peaks were determined at the Cz electrode with an average reference and re-referenced to linked mastoids (Fig. 2).

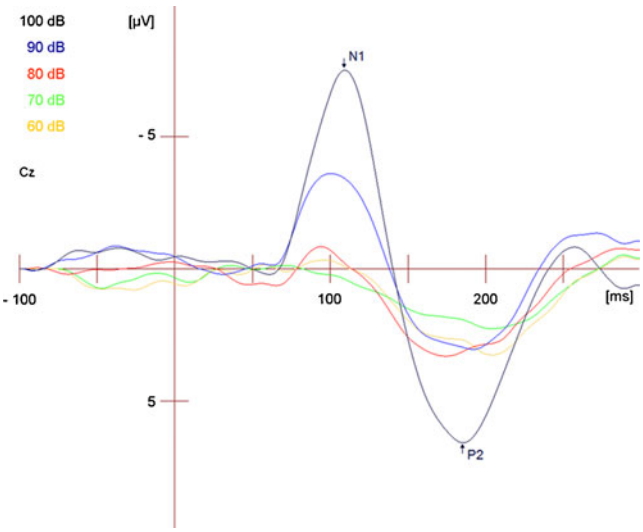

Fig. 2 Example of single subject auditory evoked potentials following stimulation with different sound pressure levels (60 to 100 dB). Single electrode data from Cz

LDAEP processing

The LDAEP is the median of all slopes of each possible connection between the five different N1/P2 amplitudes corresponding to the five different intensities. The LDAEPs of the tangential dipole activity as well the LDAEPs computed of the Cz electrodes were used as the main variables for statistical evaluation. A recent publication underlines the need for processing both the data from single electrode estimation and DSA (Hagenmuller et al. 2011). The data were un-blinded after processing of the DSA and the identification of the N1 and P2 peaks in the DSA- and single-electrode data.

Statistical analysis

The data of one participant of the male levodopa group was removed due to extreme values. The remaining variables were analyzed for normal distribution with the Kolmogorov–Smirnov test. Group differences (levodopa vs. placebo) were assessed by unpaired *t* tests. Differences between the two measurements within the groups were tested with paired *t* tests.

Results

Kolmogorov–Smirnov test revealed a normal distribution for LDAEP measurements at baseline for the single electrode estimation data (mean 0.11 µV, SD 0.075 µV, p .458) as well as the DSA data (left tangential source: mean, 1.039 nA/m; SD, 0.767 nA/m; p .87; right tangential source mean, 1.212 nA/m; SD, 0.949 nA/m; p .54).

After unblinding the data, it turned out that there were 11 females and nine males in the levodopa group and ten females and 11 males in the placebo group.

No significant differences within the groups were found, independently of the application of levodopa or placebo, gender or the use of single electrode estimation or DSA (Table 1; Figs. 3 and 4).

Table 1 Within-group differences of N1/P2 slopes (expressed as mean ± SD): paired *t* test (two-tailed) for within-group differences (within the levodopa and placebo groups) between baseline and post intervention measurement

	Dipole ((nA/m)/10 dB)		Cz ($_u$V/10 dB)
	Right	Left	
Levodopa group	0.074±1.07	0.098±0.58	0.008±0.34
Placebo group	0.009±0.36	0.004±0.56	0.005±0.04

Cz indicates data from single electrode estimation, dipole (e.g. left dipole) means the tangential dipoles

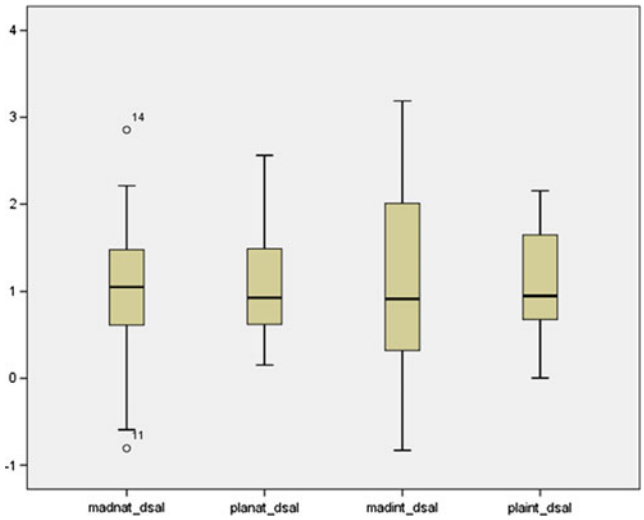

Fig. 3 *Boxplot* showing dipole source strengths [nA/m] of levodopa and placebo group for the left dipole source (*mad* levodopa, *pla* placebo, *nat* baseline measurement, *int* intervention, *dsal* dipole source analysis left)

Irrespective of the estimation method or the time point of the measurement (Table 2), no significant differences in the LDAEP were found between the groups.

The test–retest reliability (Cronbachs Alpha) between the baseline measurement and the intervention group was 0.964 (levodopa) and 0.9 (placebo) for the Cz-estimation and 0.911 (levodopa left tangential dipole), 0.67 (levodopa right tangential dipole), 0.759 (placebo left tangential dipole) 0.923 (placebo right tangential dipole).

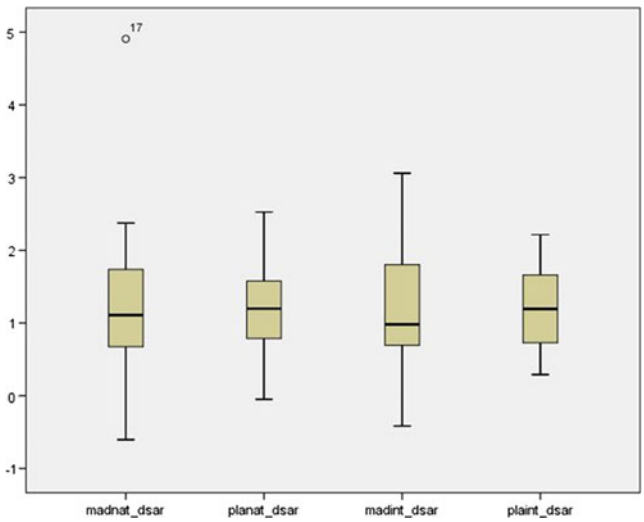

Fig. 4 *Boxplot* showing dipole source strengths [nA/m] of levodopa and placebo group for the right dipole source (*mad* levodopa, *pla* placebo, *nat* baseline measurement, *int* intervention, *dsar* dipole source analysis right)

Discussion

We had hypothesized that the acute synaptic dopamine excess caused by levodopa intake is associated with an intraindividual decrease of the LDAEP. In contrast to this hypothesis, a difference between the baseline measurement and the intervention was neither found in the levodopa nor in the placebo group. Hence, a synaptic dopaminergic excess caused by levodopa intake did not lead to an acute LDAEP alteration. Furthermore, the test–retest reliability between the baseline measurement and the intervention group states a high correlation between the two measurement conditions. Despite our negative result, the high test–retest reliability between the baseline and intervention group strengthens the LDAEP as a reliable neurophysiologic parameter with high individual stability.

We can only speculate about the cause for the increase in variance of the left dipole source after challenge with levodopa (Fig. 3). In the levodopa intervention group, some volunteers presented with nausea, which may have affected the data quality. However, this does not explain the exclusive increase in the left dipole. Another trial of our group (Wyss 2009) shows similar findings; in patients with schizophrenia, a larger variance in the amplitudes of left source waveforms was found. The healthy control group, however, showed no such increased variance. It is conceivable that a dopaminergic influence on the LDAEP exists in single subjects which only shows in a variance increase and not in the mean of the data. Assuming such an individual sensitivity exists, an examination of parameters influencing the LDAEP such as the COMT polymorphism would be interesting. Our result stands in line with other findings in the literature; O'Neill et al. (O'Neill et al. 2006, 2008b) did not find any effect of acute dopamine receptor stimulation with pergolide or bromocriptine on the LDAEP. In the studies using dopamine receptor agonists and in our trial an iatrogenic condition as a state factor is used. So far studies suggesting a dopaminergic influence on the LDAEP (Juckel et al. 2008b; Kawohl et al. 2008a; Pogarell et al. 2004) show an association of the LDAEP with trait factors, i.e. genetic variants in dopamine pathways. The LDAEP may rather present a chronic condition dependent on genetic polymorphisms associated with the 5-HT/dopamine system (O'Neill et al. 2008a). In line with this is a recent study by Lee (Lee et al. 2010) using SPECT to approximate the availability of DATs and SERTs. It provided further evidence for the possible involvement of dopamine and serotonin in the genesis of LDAEP. The correlation between monoamine transporter availability and LDAEP could reflect the long-term monoaminergic activity.

Table 2 Between-group differences (expressed as mean: mean difference, standard: standard error difference); unpaired *t* test (two-tailed) for differences between the placebo and the levodopa group (baseline and intervention)

		Dipole				Cz	
		Right		Left			
		Mean	Standard	Mean	Standard	Mean	Standard
Baseline	Equal variances	−0.19	0.30	0.05	0.24	−0.03	0.02
	Unequal variances	−0.20	0.30	0.05	0.24	−0.03	0.02
Intervention	Equal variances	−0.12	0.30	−0.01	0.30	−0.04	0.03
	Unequal variances	−0.12	0.30	−0.01	0.30	−0.04	0.03

Cz indicates data from single electrode estimation, dipole (e.g. left dipole) means the tangential dipoles

Another recent study revealed an effect of a chronic modulation of serotonergic neurotransmission on the LDAEP (Simmons et al. 2011).

The LDAEP may therefore be considered to be a chronic indicator of the 5-HT system and possibly the dopamine system. Further studies are needed to determine if this also applies for the dopamine system. This condition may be robust against short-term changes in neurotransmission, particularly dosages used in neuropsychopharmacology (Norra et al. 2008; O'Neill et al. 2008a). Thus, it seems questionable whether the LDAEP can actually be influenced by short challenge trials in humans. Considering the LDAEP as a chronic parameter, there is evidence supporting a positive relationship between personality traits such as sensation seeking as well as impulsivity and the LDAEP; higher scores on measures of sensation seeking have been reported to be associated with an increased LDAEP and possibly a lower 5-HT function (Brocke et al. 2000). Norra et al. found a correlation between an increased LDAEP and aspects of impulsiveness in patients with borderline personality (Norra et al. 2003). Interestingly, dopaminergic dysfunction seems to play an important role in borderline personality disorder, affecting traits such as impulsivity. Dopamine receptor polymorphism have been associated with traits such as novelty seeking (Ebstein et al. 2000; O'Neill et al. 2008a). In line with the aforementioned supposition of the LDAEP acting as a chronic marker of 5-HT functioning is the finding of the individual LDAEP in depressed patients not being altered after medical treatment with a selective serotonin reuptake inhibitor (SSRI) (Gallinat et al. 2000; Lee et al. 2005) after clinical improvement of depressed symptoms. It has been shown that general anxiety disorder (GAD) patients with a stronger pretreatment LDAEP show a better response to a treatment with the SSRI escitalopram (Park et al. 2011). Measurement of the LDAEP was said to provide useful clinical information for predicting treatment responses in patients with GAD. Juckel et al. (Juckel et al. 2008a) postulate that the LDAEP may be more closely related to genetic variants controlling the 5-HT release (5-HT auto receptors) and synthesis (tryptophan hydroxylase) rather than the reuptake. In a study by the same study group, 5-HT_{1B} alleles were reported to be associated with an increased LDAEP (Juckel et al. 2008a). The 5-HT_{1B} receptor is located presynaptically on serotonergic axon terminals. It occurs in high densities in the primary auditory cortex and in the brainstem raphe nuclei (Moret and Briley 2000). In addition to controlling 5-HT release in terminal areas, this receptor inhibits the release and synthesis of 5-HT and reduces the firing rate of serotonergic neurons via a negative feedback loop in the raphe nuclei (Moret and Briley 2000). Interestingly, 5-HT_{1B} receptors can also function as a heteroreceptor at non-serotonergic neurons controlling the release of neurotransmitters other than 5-HT (such as dopamine, acetylcholine and glutamate) (Moret and Briley 2000). Thus, the 5-HT and dopamine interactions and their possibly influence on the LDAEP may be complex.

Our study is not without limitations. Ideally, blood samples should have been taken to estimate the individual levodopa blood levels at its estimated t_{max} of 60 min after oral intake. Due to practical reasons, we refrained from conducting a crossover study. Nevertheless, we do not expect any additional outcome by such a design. Other limitations regarding the statistical power are the rather small sample size and low dosage of levodopa. Possibly a higher dosage of levodopa or a bigger sample size could have shown different results. Nevertheless, based upon our data, a number of 3,124 persons per group would be needed (power 0.9) in order to show significance within group differences given these results. This is clearly not practicable. On the other hand, our sample size would have been large enough to detect a moderate effect of 0.5 with a power of 48.2% or a larger effect of 0.8 with a power of 82% (Cohen 1992). Additionally, other dopaminergic influences associated with the LDAEP like the *COMT* polymorphism could have been examined.

Conclusion

Our study shows an absence of acute dopaminergic influence due to a single intake of levodopa on the LDAEP. Our findings are in agreement with the findings of O`Neill et al. (O'Neill et al. 2006, 2008b) stating the absence of acute dopaminergic influence on the LDAEP. To our knowledge, our study is the first trial having computed the data via dipole source analysis and Cz estimation.

As dopamine possibly may be a chronic parameter concerning the LDAEP, studies with, e.g. longer dopamine intake in healthy volunteers may be needed to examine a dopaminergic influence on the LDAEP.

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